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FINNEGAN, HENDERSON, FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET N.W.
WASHINGTON, DC 20005

EXAMINER

RAMIREZ, DELIA M

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 05/06/2003

33

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/957,709

Applicant(s)

HOGREFE ET AL.

Examiner

Delia M. Ramirez

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 3/10/2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17,24-27,40-44,46-95 and 97 is/are pending in the application.
- 4a) Of the above claim(s) 24-27,40-44,47-58,67-76,81-84,86,93 and 94 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17,46,59-66,77-80,85,87-92,95 and 97 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 March 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 29.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 17, 24-27, 40-44, 46-95 and 97 are pending.

Applicant's amendment of claims 17, 46, 59-66, 77-80, 85, 90, 95, cancellation of claims 9, 16, and 96, in Paper No. 32, filed on 3/10/2003 is acknowledged.

As indicated in previous Office Action Paper No. 28, mailed on 10/8/2002, claims 24-27, 40-44, 47-58, 67-76, 81-84, 86, 93-94 were withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to an invention non-elected without traverse in Paper No. 9, filed 6/21/01. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 1/16/2003 was filed after the mailing date of Office Action Paper No. 28 on 10/8/2002. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

2. The specification is objected to for the following reasons. The alignment in page 43 is not formatted within the appropriate margins. When the application pages were perforated, text

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was lost. Furthermore, the alignment in page 43 is objected to since it contains solid black shading areas. See 37 CFR 1.84(m). Appropriate correction is required.

Drawings

3. The formal drawings submitted 3/10/2003 have been reviewed and are approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Objections

4. Claim 90 is objected to because of the recitation of "Pfu". For clarity, it is suggested that the term "P. furiosus" be added to the claim to clearly indicate that the term Pfu refers to P. furiosus. Appropriate correction is required.

5. Claim 95 is objected to because of the recitation of "nucleic acid that hybridizes to the complement of the nucleotide sequence". For clarity, it is suggested that the term "sequence" be deleted since as known in the art, hybridization occurs among nucleic acids. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 17, 46 and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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8. Claims 17 is indefinite in the recitation of “at least one subunit is a *P. furiosus* protein selected from at least one of” for the following reasons. As written, the term “selected from at least one of” implies that the *P. furiosus* protein can be a combination of several proteins, i.e. the ones recited immediately after the term “at least one of”, which is unclear and confusing since it appears from the preamble that the *P. furiosus* protein is a single protein and not a mixture. It is suggested that the term “selected from at least one of” be replaced with “selected from the group consisting of” if the *P. furiosus* protein is a single protein and not a mixture. For examination purposes, the term “selected from the group consisting of” will be used instead. Correction is required.

9. Claim 46 is indefinite in the recitation of “at least one of SEQ ID NO: 19 and 71” since as written, the term “at least one of” implies that the antibody can bind to a protein comprising both SEQ ID NO: 19 and SEQ ID NO: 71. It is suggested that if the antibody can bind to a protein comprising the sequence of SEQ ID NO: 19 or a protein comprising the sequence of SEQ ID NO: 71, the claim be amended accordingly. For examination purposes, it will be assumed that the claimed antibody can bind (1) a protein comprising the sequence of SEQ ID NO: 19, or (2) a protein comprising the sequence of SEQ ID NO: 71. Correction is required.

10. Claim 80 is indefinite in the recitation of “wherein the protein is an analog protein” for the following reasons. First, it is unclear which analog protein is being recited since there is no indication of which protein is being used for determining analogy, i.e. what is the protein an analog of. Second, one cannot determine the basis of analogy. As written, it is unclear if “analog protein” refers to a protein of the same size, same function, similar 3D structure, etc.

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For examination purposes, it will be assumed that the term “analog protein” means “any protein”. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 80, 87-92 and 97 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. This rejection, as applied to claims 80, 87-92 and 97 has been discussed at length in Paper No. 28, mailed 10/8/2002.

14. Applicants argue that the amendments made to claim 77, from which claim 80 is dependent upon should obviate the rejection in regard to claim 80. In regard to claims 87-92 and 97, Applicants argue that the specification discloses the use of a *T. thermophilis* dUTPase enzyme, demonstration of dUTPase activity in *T. thermophilis* and regions of identity/similarity between P45 and several dUTPases. Thus, Applicants request reconsideration and withdrawal of the rejection as it applies to claims 87-92 and 97.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. While Applicant's amendment of claim 77 is acknowledged, the scope of amended claim 80 encompasses a composition comprising any protein. See claim rejections

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under 35 USC 112, second paragraph for claim interpretation. While the specification discloses the polypeptide of SEQ ID NO: 71, its possible function as a dUTPase/dCTPase and its effect on DNA polymerase, the specification does not disclose proteins of other functions or their structures, as encompassed by claim 80. Furthermore, the specification does not disclose the critical structural elements required in a dUTPase or a dCTPase which would result in polymerase enhancing activity. In regard to claims 87-92 and 97, while the Examiner agrees that the specification discloses the determination of dUTPase activity in a *T. thermophilis* cell extract and the detection in a Western blot of a protein in that cell extract using an antibody against the *P. furiosus* protein P45 of SEQ ID NO: 71, the specification fails to disclose the isolation of a *T. thermophilis* dUTPase or its amino acid structure. It is noted that a *T. thermophilis* dUTPase is required in the claimed protein extract. While the Examiner agrees that the specification discloses the alignment of several dUTPases with the *P. furiosus* P45 protein of SEQ ID NO: 71, it is noted that there is no indication as to whether the regions of similarity /identity found correlate with dUTPase activity or if they are characteristic of dUTPases. Furthermore, it is noted that according to the specification, the polypeptide of SEQ ID NO: 71 from *P. furiosus* has higher amino acid sequence homology to a dCTPase than a dUTPase. Therefore, one cannot reasonably determine the function of a *T. thermophilis* polypeptide which comprises the regions of similarity/identity indicated by Applicants based solely on structural homology since there is no information as to whether these regions are indeed indicative of dUTPase activity.

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16. Claim 85 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 85 is directed to a genus of proteins having polymerase enhancing factor activity wherein the proteins comprise the peptide of SEQ ID NO: 73. An adequate description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. The recited structural feature of the genera (i.e. polypeptide comprising the peptide of SEQ ID NO: 73) does not constitute a substantial portion of the genus since the remainder of the structure of any polypeptide having polymerase enhancing activity is completely undefined and the specification does not provide the remaining structural features necessary for members of the genus to be selected. While the specification discloses that the peptide (14 amino acids) of SEQ ID NO: 73 is a putative uridine binding domain, neither the specification nor the prior art discloses any correlation between the peptide of SEQ ID NO: 73 and polymerase enhancing activity. As indicated in previous Office Action Paper No. 28, the state of the art teaches that small structural changes can result in drastic functional changes. See the teachings of Van de Loo et al. and Broun et al. already discussed. Furthermore, Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teach that even polypeptides which share an extremely large degree of structural homology do not share the same function. Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino

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acid substitution transforms a β -ketoacyl synthase into a malonyl decarboxylase and completely eliminates β -ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. In the instant case, the polypeptides claimed share only 14 consecutive amino acids (SEQ ID NO: 73), therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicants are referred to the revised guidelines concerning compliance with the written description requirement of 35 USC 112, first paragraph, published in the Official Gazette and also available at the USPTO website.

17. Claims 80, 85, 87-92, and 97 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 71, does not reasonably provide enablement for (1) a composition comprising any protein, (2) a composition comprising a functional analog of the polypeptide of SEQ ID NO: 71, or (3) a composition or protein extract comprising a *T. thermophilis* dUTPase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

18. This rejection, as applied to claims 80, 85, 87-92 and 97 has been discussed at length in Paper No. 28, mailed 10/8/2002.

19. Applicants argue that the Examiner provides no particular reasons why isolation of polypeptides, analogs or protein extracts is not routine in the art. Applicants submit that at the

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time the invention was made, several commercial ventures produced chromatography columns, cloning kits and reagents used in the isolation of polypeptides and protein complexes.

Applicants further argue that a screening assay for polymerase enhancing activity is described. Therefore, it is Applicant's contention that it would not require undue experimentation to determine whether any single protein having the peptide of SEQ ID NO: 73 displays polymerase enhancing activity. In regard to claim 80, Applicants submit that amendment of claim 77 should render the rejection against claim 80 moot. In regard to claims 87-92 and 97, Applicants argue that the specification discusses dUTPase activity in *T. thermophilis* samples and binding of an antibody against the *P. furiosus* protein of SEQ ID NO: 71 to a protein in a *T. thermophilis* sample. It is Applicant's opinion that the Examiner has not established that it would require undue experimentation for one of skill in the art to determine if a protein bound in the band was responsible for the detected dUTPase activity and that dUTPase activity does not require knowing any of the critical structural elements of a dUTPase.

20. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection as it applies to claims 80, 85, 87-92, and 97. The Examiner acknowledges Applicant's amendment of claim 77, however, claim 80 as amended is now drawn to a composition comprising a protein of any function. See claim rejections under 35 USC 112, second paragraph for claim interpretation. While the Examiner agrees that (1) chromatography columns, cloning kits and reagents to isolate polypeptides were available at the time the invention was filed, and (2) the specification provides an assay to determine polymerase enhancing activity, the specification fails to disclose the functions and structures of the proteins encompassed by claim 80. Determining unknown function and unknown structures without any

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guidance would constitute undue experimentation. Furthermore, even if the proteins of claim 80 are functional analogs of the polypeptide of SEQ ID NO: 71, it is noted that while testing a limited number of samples would not constitute undue experimentation, the full scope of the claim encompasses an unlimited number of proteins. Similarly, while testing a limited number of polypeptides having the peptide of SEQ ID NO: 73 would not constitute undue experimentation, the claim encompasses any protein which comprises the 14-amino acid peptide, therefore the number of samples to test is extremely large. As indicated above, there is no disclosure of critical structural elements indicative of polymerase enhancing activity, therefore one of skill in the art would have to go through the burden of undue experimentation to test an extremely large number of samples. In regard to claims 87-92 and 97, the Examiner acknowledges the disclosure of the determination of dUTPase activity in a *T. thermophilis* cell extract and the detection in a Western blot of a protein in that cell extract using an antibody against the *P. furiosus* protein P45 of SEQ ID NO: 71, however the Examiner disagrees with Applicant's contention that isolating the *T. thermophilis* dUTPase would not constitute undue experimentation with the information provided by the disclosure. The protein extract claimed requires a purified *T. thermophilis* dUTPase. Applicants have disclosed that an unspecified antibody raised against the polypeptide of SEQ ID NO: 71 can detect proteins in a Western blot having a *T. thermophilis* cell extract. Since the specification is silent in regard to the critical structural elements required in a dUTPase and does not provide any clue as to which regions of the polypeptide of SEQ ID NO: 71 correlate with this activity, the antibody against the polypeptide of SEQ ID NO: 71 described in the specification may not target a polypeptide having dUTPase function since the epitope which corresponds to that antibody may not be one

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which correlates with dUTPase activity. While one could argue that the number of proteins which would be targeted by such antibody may be small, it is noted that protein purification is not trivial in the art and one may require structural information to determine the best chromatography approach to achieve its purification. While one could argue that one may use (1) the regions of similarity/identity disclosed by Applicants in regard to the polypeptide of SEQ ID NO: 71 and dUTPases, or (2) the structure of the polypeptide of SEQ ID NO: 71 as additional structural information, it is noted that the specification discloses that there is higher structural homology between the polypeptide of SEQ ID NO: 71 and dCTPases than there is with dUTPases. Therefore, in view of the information provided, one cannot reasonably conclude that the specification enables the full scope of the instant claims.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

21. Claim 80 is rejected under 35 U.S.C. 102(a) as being anticipated by Cohen et al. (Genomics 40(1):213-215, February 15, 1997; GenBank accession number U62891 (DNA) and AAC51123 (protein)) as evidenced by Hogrefe et al. (Proc. Natl. Acad. Sci. 99(2):596-601, 2002; cited in the IDS). Cohen et al. teaches a human dUTPase (dUTP pyrophosphatase) which has polymerase enhancing activity as evidenced by Hogrefe et al. (page 597, first column, Cloning and preparation of recombinant proteins; page 599, column 1, Human dUTPase has PCR-enhancing activity). Claim 80 is drawn to a composition comprising any protein including functional analogs of the polypeptide of SEQ ID NO: 71. Therefore, the polypeptide of Cohen et al. anticipate the claim as written.

Double Patenting

22. Claims 17, 46, 59-66, 77-80, 85, 87-92, 95, and 97 were rejected under the judicially created doctrine of double patenting over claims 1, 5-9, 13-20, 23-24, 26-34 and 40-41 over U.S. Patent No. 6,183,997.

23. This rejection has been discussed at length in Paper No. 25, mailed on 2/27/2002.

24. Applicants have indicated that if the instant claims are found allowable, a terminal disclaimer will be filed. Since a terminal disclaimer has not yet been filed and no arguments have been presented pointing out disagreements with the Examiner's contentions, the double patenting rejection is maintained for the reasons of record.

Allowable Subject Matter

25. Claims 17, 46, 59-66, 77-79 and 95 appear to be allowable over the prior art of record and would be allowable if the appropriate action is taken to overcome the objections, double patenting rejection(s), and rejection(s) under 35 USC 112, second paragraph set forth in this Office Action.

Conclusion

26. No claim is in condition for allowance.

27. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

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28. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 30, 2003


REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1602
1602